

## Improving management of diabetic kidney disease

Bellary, Srikanth; Tahrani, Abd; Barnett, Anthony H.

DOI:

[10.1016/S2213-8587\(20\)30301-6](https://doi.org/10.1016/S2213-8587(20)30301-6)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Bellary, S, Tahrani, A & Barnett, AH 2020, 'Improving management of diabetic kidney disease: will GLP-1 receptor agonists have a role?', *The Lancet Diabetes and Endocrinology*, vol. 8, no. 11, pp. 870-871.  
[https://doi.org/10.1016/S2213-8587\(20\)30301-6](https://doi.org/10.1016/S2213-8587(20)30301-6)

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Manuscript type: Commentary

## **Improving Management of Diabetic Kidney Disease-will GLP-1 Receptor Agonists have a role?**

Authors and affiliations: Srikanth Bellary <sup>1,2</sup>, Abd A Tahrani <sup>2,3,4</sup>, Anthony H Barnett<sup>2,3</sup>

1. School of Life and Health Sciences, Aston University, Birmingham, UK
2. University Hospitals Birmingham NHS Foundation Trust, Birmingham
3. Institute of Metabolism and Systems Research, University of Birmingham, UK
4. Centre for Endocrinology Diabetes and Metabolism (CEDAM), Birmingham Health Partners, Birmingham, UK

Corresponding author:

Dr Srikanth Bellary  
Reader, Aston University  
Birmingham, UK  
B4 7ET

Email: [s.bellary@aston.ac.uk](mailto:s.bellary@aston.ac.uk)  
Tel: 0121 204 4145

Word count: 861 words

## Improving Management of Diabetic Kidney Disease-will GLP-1 Receptor Agonists have a role?

Renal disease will affect around 40% of people with type 2 diabetes (T2D) and is a leading cause of morbidity and mortality(1).Management of Diabetic Kidney Disease (DKD) has traditionally focused on tight glycaemic (in the early stages ) and blood pressure control the latter including agents which inhibit the renin-angiotensin system(1).Despite this, most patients with DKD experience a gradual decline in renal function eventually progressing to end stage renal disease and an increased risk of cardiovascular events and mortality. Glucagon like peptide-1 receptor agonists (GLP1-RAs) are established treatments for T2D which, in addition to glucose lowering, are associated with weight loss, blood pressure lowering and cardio-protection (2). There is a lack of clarity, however, on the long-term benefits of GLP-1RA therapy in DKD particularly in relation to glomerular function.

In their paper published in the Lancet D and E, Mann et al (3), report a post-hoc analysis of changes over a period of 30 weeks in glomerular function, albuminuria and safety from pooled data from SUSTAIN (1-5 and 7) studies and then separately from the longer term Cardiovascular Outcome Trial-SUSTAIN 6 (4). The GLP-1 RA, semaglutide, was associated with : (a) a fall in eGFR of 2.5 to 3.5ml/min during the first 12 weeks followed by stabilisation between 12-30 weeks in those with baseline eGFR >60ml/min, but less marked in those with significant renal impairment (b) a consistent and significant decrease in albuminuria more pronounced in those with established albuminuria (c) no excess risk of major renal adverse events including acute renal injury or urinary disorders.

Currently, most evidence for renal protection with GLP1-RAs comes from cardiovascular outcome trials (CVOTs)(5-7). Pre-specified sub-group analysis of data from these studies have shown an overall reduction in composite renal outcomes (incidence and progression of albuminuria, doubling of serum creatinine, requirement for renal replacement therapy and renal death). The reported benefits were mainly driven by a gradual reduction in albuminuria with only a minimal effect on glomerular function. The more acute fall in eGFR followed by evidence of stabilisation reported by Mann et al and seen in each of the individual SUSTAIN trials is surprising and not previously noted with GLP1-RA therapy.

Haemodynamic alterations following treatment with renin angiotensin and SGLT2 inhibitors are well recognized(8) .The resulting decrease in glomerular pressure has been associated

with prevention and/or reduction of albuminuria and delay in progression of DKD. This is therefore an area of significant interest in relation to GLP-1 RA therapy where the LEADER trial (6) and the exploratory analysis of the REWIND study (5) have previously reported significant reductions in albuminuria independent of glycaemic and blood pressure control with liraglutide and dulaglutide respectively. The findings of the present study suggest a similar reduction in albuminuria with semaglutide. Given that increasing levels of albuminuria are poor prognostic markers in DKD, such reductions in albuminuria with GLP-1 RAs are of interest, but emphasise the need for more studies to determine whether this is reflected in renal protection long term.

Whilst the inclusion of a large number of subjects and the consistency of the findings can be seen as a strength, a major limitation of this post-hoc analysis is that it is based on data pooled from different studies. This imposes restrictions on analysis and interpretation of the findings. For example, there is a significant degree of heterogeneity between the cohorts plus varying durations of follow up. Moreover, limiting duration of follow up to only 30 weeks is insufficient to provide information on the effects of semaglutide on progression of DKD and indeed on long term safety. It could be argued, however, that given the patient cohorts include those with large ranges of eGFR and albuminuria, this allows for a better understanding of the effects of semaglutide at different stages and severity of DKD. In addition, the findings that semaglutide was not associated with an increase in renal adverse events and particularly acute kidney injury or urinary disorders provide reassurance regarding its use for its primary indications.

Whilst these findings may be seen as highly relevant in the context of management of T2D and specifically in prevention and progression of associated DKD, significant questions remain. Reductions in albuminuria and hemodynamic changes affecting glomerular function are recognised markers indicating reno-protection, but DKD progresses over many years and there is little evidence whether these improvements will translate into reduction of progression to ESRD. Hopefully this critical point will be answered by the ongoing renal outcome studies such as Semaglutide Renal Outcomes Trial (FLOW).

Another question relates to establishing the role and positioning of GLP1-RA treatment in the management of DKD. For example, an agent from a different class of anti-diabetes therapies, the SGLT-2 inhibitor canagliflozin, effectively improves all renal outcomes (9) and studies

involving others in the class indicating similar benefits (10). To more clearly define the place of these agents in management, an understanding of the exact mechanisms through which SGLT2i and GLP1-RA exert their renal effects needs to be elucidated. If the mechanisms are different, could they have a complimentary role? Finally, despite the limitations of this type of analysis, these findings offer some reassurance and confidence in the use of GLP1-RA in patients with, or at risk of, DKD.

.

## References

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clinical journal of the American Society of Nephrology : CJASN*. 2017;12(12):2032-45.
2. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr*. 2017;30(3):202-10.
3. Mann JF, Hansen T, Idorn T, Leiter LA, Marso SP, Rossing P, et al. Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: analysis of the SUSTAIN 1–7 randomised controlled trials. *The Lancet Diabetes and Endocrinology*. 2020;XX(XX):XX.
4. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-44.
5. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet (London, England)*. 2019;394(10193):131-8.
6. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(9):839-48.
7. Musket MHA, Tonneijck L, Huang Y, Liu M, Saremi A, Heerspink HJL, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):859-69.
8. Skrtic M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. *Curr Opin Nephrol Hypertens*. 2015;24(1):96-103.
9. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-306.
10. <https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-phase-iii-dapa-ckd-trial-will-be-stopped-early-after-overwhelming-efficacy-in-patients-with-chronic-kidney-disease.html>. Date accessed : 12 August 2020